IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Confirmation No.: 7774
DROHAN *et al.*	Art Unit: 1631
Appl. No. 08/479,038	Examiner: Marschel, Ardin H.
Filed: June 7, 1995	Atty. Docket: 1327.0440006/ELE/LAV
For: **Supplemented Fibrin Matrix Delivery Systems** (*as amended*)	

Declaration Under 37 C.F.R. § 1.132

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

Sir:

I, the undersigned, Dr. Julia Lathrop, residing at 1000 Poplar Drive, Falls Church, VA 22046, declare and state as follows:

1. My education and professional experience are set forth on the attached copy of my resume (Exhibit A).

2. I have read and understand the specification and claims of United States Patent Application No. 08/479,038, filed June 7, 1995 in the name of William N. Drohan *et al.* for SUPPLEMENTED FIBRIN MATRIX DELIVERY SYSTEMS (*as amended*). I have also reviewed and understand the Office Action dated July 13, 2005, as well as the presently pending claims.

3. As stated on my resume, as a part of my responsibilities at the American Red Cross, I have been involved in the development of fibrin sealant matrices as a delivery system for drugs and/or biologics.

4. On October 6, 2004, I attended an interview with Examiner Marschel at the United States Patent and Trademark Office. At that interview, I discussed the delivery of supplements from fibrin sealant (and tissue sealants generally) with Examiner Marschel. We also discussed the delivery kinetics of various supplements in fibrin sealant matrices.

5. The invention claimed in the patent application relates to the field of tissue sealants. More particularly, the invention relates to the art or field of production and use of tissue sealants which have been supplemented with growth factor(s) and/or drug(s). In my opinion, a person of ordinary skill in the field of tissue sealant technology would have a degree in biology or a field related to biology.

6. The claimed invention is directed to a supplement delivery system comprising an effective amount of at least one supplement and a biocompatible tissue sealant comprising fibrinogen in an amount which forms a fibrin matrix; wherein the fibrinogen will form a fibrin matrix when in the presence of thrombin and Ca^{++} and water; and further wherein the supplement is delivered from the fibrin matrix into the external environment of use for a sustained period; and further wherein the amount of the supplement is greater than the amount which is soluble in said fibrin matrix; and further wherein the composition is substantially free of added protease inhibitors; and further wherein said sustained period is

greater than the period obtained when the amount of the supplement is soluble in the fibrin matrix; and further wherein said fibrin matrix is substantially free of liposomes.

7. It is my understanding, as explained to me by the American Red Cross's patent attorneys, that an objective standard for determining compliance with the written description requirement of 35 U.S.C. §112, first paragraph is whether, as of the filing date, the inventor conveyed with reasonable clarity to those of skill in the art that he was in possession of the subject matter of the claims. It is also my understanding that an applicant may show possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structure, figures, diagrams, and formulas that fully set forth the claimed invention.

8. Using this standard of the written description requirement, it is my view that the disclosure of U.S. Application No. 08/479,038, and priority U.S. Application Nos. 08/351,006, filed December 7, 1994, 08/328,552, filed October 24, 1994, and 08/031,164, filed March 12, 1993, convey with reasonable clarity to those of skill in the art that the inventors were in possession of the subject matter of the claims. Specifically, it is my opinion that a person of ordinary skill in the art, upon reviewing the entire specification, including the figures and examples, would recognize that the claimed supplement delivery system will deliver the supplement from the fibrin matrix for a sustained period when the supplement is loaded into fibrin matrix above its solubility limit. It is further my opinion that a person of ordinary skill in the art, after reviewing the entire specification would understand that such a sustained period is of greater duration than the period obtained when

the amount of supplement is soluble in the fibrin matrix. Below is a brief discussion of some of the Figures and Examples that provide written descriptive support for the claimed invention:

a) Figure 23 shows release of TET from a fibrin matrix for approximately two to three weeks when loaded above its solubility limit (100 mg/ml and 200 mg/ml), as compared to the release of TET for five days or less when loaded below its solubility limit (50 mg/ml).

b) Figure 24 shows delivery of TET for 13 days from a fibrin matrix when loaded above its solubility limits (100 mg/ml).

c) Figure 28 shows sustained release of CIP from fibrin matrix when loaded above its solubility limit.

d) Figure 31(a) shows sustained release of CIP and TET from fibrin matrix for 14 days and 42 days, respectively, when loaded above their solubility limits.

e) Figure 32 shows sustained delivery of 5-FU from a fibrin matrix when loaded above the solubility limit as compared to 5-FU loaded in an amount that is soluble.

f) Example 19 describes the sustained release of antimicrobial compositions from a fibrin matrix and notes the correlation between the long term delivery of antibiotics and solubility.

g) Example 20 describes sustained release of 5-FU from a fibrin matrix when loaded above its solubility limit (50 mg/disk) as compared to the immediate release of 5-FU from a fibrin matrix when loaded at or below its solubility limit (7 mg/disk). It also predicts that including even more 5-FU in the fibrin matrix will result in even longer drug delivery times.

h) Example 21 describes the sustained delivery of taxol or paclitaxel from a fibrin matrix by loading a mass of drug that exceeds its solubility in the matrix volume. ("These experiments showed that long term delivery of taxol from a supplemented fibrin sealant composition can be accomplished by loading a mass of drug that exceeds its solubility in the matrix volume." page 110).

9. It is my opinion that a person of ordinary skill in the art would know and understand that the solubility limit of a supplement in a particular medium is the amount of supplement that will dissolve in the medium under normal conditions. It is also my opinion that a person of ordinary skill in the art would know and understand that one way to determine the solubility limit of a particular medium, such as fibrin sealant, is to add the supplement to the medium until that supplement no longer remains in solution or dissolves in the medium, but instead precipitates out of solution.

10. In conjunction with my discussion of the delivery kinetics of supplemented fibrin sealant matrices during the October 6, 2004 interview, a series of slides were displayed. A copy of each of the slides in the series that was displayed at the interview is attached to this Declaration (Exhibit B). Below each slide is a brief description of the content thereof and its relevance to the delivery kinetics of supplemented fibrin sealant matrices, as prepared by Dr. Stanley A. Friedman. I have highlighted portions of the slides in this Declaration:

a) Slide 7, which corresponds to Figure 32 of the present application, shows that loading a drug into fibrin sealant above its solubility limit significantly extends its release. Slide 7 shows release of 5-FU in fibrin sealant when loaded at its saturation point (solubility limit) as compared to 5-FU loaded into fibrin sealant above its saturation point. The graph shows that when the 5-FU is loaded into the fibrin sealant at its saturation limit, it is rapidly released into the external environment almost immediately, and after 10 hours, there is almost no measurable release of supplement from the fibrin sealant. The graph also shows that when the 5-FU is loaded into the fibrin sealant above its solubility limit, the release is extended to at least 50 hours. Thus, when the 5-FU is loaded into the fibrin matrix above its solubility limit, the period of release is longer than the period obtained when the 5-FU is soluble in the fibrin matrix.

b) Slide 9 corresponds to Figure 31(a) of the present application, and shows the long term delivery of two different antibiotics by loading them above their solubility limits in fibrin sealant. The data shows that the American Red Cross was able to deliver a therapeutic dose of drugs for weeks.

11. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the present patent application or any patent issued thereon.

Respectfully submitted,

Julia Lathrop, Ph.D.

Date: 10 January 2006

Curriculum Vitae

Julia Tait Lathrop, Ph.D.

HOME ADDRESS: 1000 Poplar Drive
Falls Church, Virginia 22046
(703) 237-1808
(301) 738-0778 (w)
lathropj@usa.redcross.org

EDUCATION:

Ph.D., Biology, University of Virginia. January, 1993. Michael P. Timko, Ph.D. advisor. Dissertation: The Regulation of In Vitro Transport of Erythroid 5-aminolevulinate Synthase into Mouse Mitochondria by Hemin. Published in *Science* 259:522-525 (Lathrop and Timko, 1993)

B.S., Biology, The College of William and Mary. May, 1982.

PROFESSIONAL EXPERIENCE:

June, 1997 – Present; Jerome Holland Laboratory, American Red Cross.

Plasma Derivatives Laboratory February 1998- present
March 2001- present; Scientist I, Scientist II (Jan. 2002)- Principle Investigator, New Product Discovery

- Responsible for conceiving, developing, and overseeing implementation of novel, disease-targeted assays for selecting therapeutic targets based on protein function. Responsibilities include budget supervision and planning, writing publications and reports, contributing to patent preparation and filing.
- Responsible for conceiving, developing, and overseeing implementation of novel screening methodologies for detection of peptide ligands for affinity purification of proteins from complex mixtures. Responsible for transfer of techniques to internal and external programs and collaborators.
- Contribute to complex, international project teams developing new manufacturing methods and pathogen removal and diagnostic technologies.
- Responsible for identification and scientific interactions with strategic partners and internal and external collaborators.
- Supervise a team of scientists and research associates who investigate multiple projects within the program.
- Responsible for development of program objectives and results, and presentation to senior management within the Holland Lab and Plasma Services.

July, 1999 - Present. Principal Investigator (March 2000), Fibrin Sealant Drug Delivery Program

- Responsible for developing and maintaining a multi-component program, the main focus of which is the development and bringing to market of a drug delivery device primarily composed of purified plasma proteins.
- Responsible for identifying, establishing, and maintaining collaborations with outside investigators, including internationally recognized physicians, surgeons, and regulatory consultants.
- Responsible for developing a project using Fibrin Sealant as an antibiotic delivery matrix for the treatment of osteomyelitis.
- Developed techniques using Fibrin Sealant as a DNA delivery vehicle to transfect mammalian cells in culture.

February 1998 - July, 1999. Research Fellow II, Scientist I (January 1999) Fibrin Sealant Bandage Program

- Improved bandage testing throughput by > 30% by developing an *ex vivo* assay that correlated with *in vivo* results.
- Formulated timelines and met milestones ahead of schedule.
- Transferred assays to a GMP manufacturing partner.
- Developed *in vitro* screening and stability assays to optimize bandage development.
- Supervised team of research assistants working on various aspects of bandage development program.
- Coordinated the American Red Cross's participation in the NIBSC's International Collaborative Study for the development of an international fibrinogen standard.

Molecular Biology Laboratory
June 1997 - February, 1998. Research Fellow I
Thomas Maciag, Ph.D., advisor.

- Studied proteins involved in the secretion of FGF-1 in mammalian tissue culture cells.

OTHER EXPERIENCE

January 1993- March 1996. Research Associate, Department of Microbiology, University of Virginia Health Sciences Center, Robert J. Kadner, Ph.D., advisor. Studied the structure and function of the *Escherichia coli* vitamin B12 receptor, BtuB.

October- December, 1992. Guest Investigator in plant circadian rhythms, Department of Biology, University of Virginia, Steve A. Kay, Ph.D., advisor. Screened cDNA libraries for temporally-specific genes using Southern, Northern, and colony hybridization techniques.

July 1983- July 1985. Laboratory Technician, Genetic Toxicology, Hazleton Biotechnologies, Inc. Conducted toxicity and mutagenicity assays of a variety of compounds in mammalian tissue culture systems.

September 1982- July 1983. AALAS-certified Laboratory Animal Technician, Chronic Rodent Toxicology, Hazleton Laboratories of America, Inc. Conducted tests on various compounds for toxicity and carcinogenicity by several techniques, including oral lavage and ingestion.

TEACHING EXPERIENCE:

January 1997- May 1997. Adjunct Assistant Professor of Biology, Department of Biology, Northern Virginia Community College, Annandale, Virginia. Had sole responsibility for a lecture and lab section of Introductory Biology. Prepared syllabus, lectures, exams, and quizzes.

August 1985- May 1992. Teaching Assistant (Developmental Biology, Introductory Biology labs), Department of Biology, University of Virginia.

Awards and Honors:

1988	Awarded a University of Virginia Biology Department fellowship for excellence in teaching (the only time this award was bestowed)
1987	Awarded the William H. Kepner Award for excellence in teaching

PATENTS:

1. Plasma Protein Binding Ligands; Hammond D.J., *Lathrop, J.T.*, Ralston, A., Hayes, T., and Fijalkowska, I. US10414, 524 and PCT/US03/11798 filed April 14, 2003.

2. Method for Identifying Ligands Specific for Structural Isoforms of Proteins; *Lathrop, J.T.*, Hammond, D.J., Cervenakova, L., Gheorghiu, L., and Yakovleva, O. US 10/823,888 filed 4/14/2004; PCT/US2004/011402 filed 4/14/04.

3. Prion Protein Ligands and Methods of Use; Hammond, D.J., Carbonell, R., *Lathrop, J.T.*, Cervenakova, L; US 10/727,335 and PCT/US03/38343 filed 12/3/2003

4. Method for Identifying Individual Active Entities from Complex Mixtures, Hammond, D.J., *Lathrop, J.T.*, Sarkar, J., and Gheorghiu, L.; US 10/601,032 and PCT/US03/19584 June 20, 2003. 20040101830

5. Method for Detecting Ligands and Targets in a Mixture, *Lathrop, J.T. and* Hammond, D. J.; US10,414,523 and PCT/US03/11799 filed April 14, 2003. 20030211471

PUBLICATIONS:

1. Thulasiraman, V.T., Lin, S., Gheorghiu, L., *Lathrop, J.T.*, Lomas, L., Hammond, D.J., Boshetti, E. (2005). Reduction of the concentration differential of proteins in biological liquids using a library of combinatorial ligands. *Electrophoresis* **26**(18):3561-3571.

2. *Lathrop, J.T.*, Carrick, K., Hayes, T.K., Hammond, D.J. (2005) "Rarity Holds a Charm": Evaluation of trace proteins in plasma and serum (invited review). *Expert Review of Proteomics* **2**(3):393-406.

3. *Lathrop, J.T.*, Anderson, N. L., Anderson, N.G., Hammond, D.J. (2003). Therapeutic potential of the plasma proteome (invited review). *Curr. Opin. Mol. Therapeu* **5**: 250 -257.

4. Mader, J. T., Stevens, C. M., Stevens, J. H., Ruble, R., *Lathrop, J.T.*, and Calhoun, J. H. (2002) Treatment of Experimental Osteomyelitis with a Fibrin Sealant Antibiotic Implant. *Clinical Orthopedics and Related Research* **403**:58-72.

5. Mouta-Carreira, C., LaVallee, T., Tarantini, F., Jackson, A., *Lathrop, J.T.*, Hampton, B., Burgess, W., and Maciag, T. (1998) S100A13 is involved in the regulation of FGF-1 and p40 Syn-1 release *in vitro*. *J. Biol. Chem.* **273**: 22224-22231.

6. Kadner, R.J., Franklund, C.V., and *Lathrop, J.T*, (1996) Communication between membranes in TonB-dependent transport across the bacterial outer membrane, *In* Handbook of Biological Physics, Vol. 2. Transport Processes in Eukaryotic and Prokaryotic Organisms. (W. N. Konigs, H. R. Kaback, and J. S. Lolkema, eds.) Elsevier Science, Amsterdam, pp. 637-663.

7. *Lathrop, J.T.,* Wei, B., Touchie, G.A., and Kadner, R.J., (1995) Sequences of the *Escherichia coli* BtuB protein essential for its insertion and function in the outer membrane. *J. Bacteriol.* **177**: 6810-6819.

8. *Lathrop, J.T.* and Timko, M.P., (1993) Regulation by heme of mitochondrial protein transport through a conserved amino acid motif. *Science* **259**:522-525.

PRESENTATIONS

1. *J.T. Lathrop*, L. Gheorghiu, S. Lin, L. Lomas, J. Sarkar, V. Thulasiraman, E. Boschetti, D. Hammond. Reducing the dynamic range of plasma using solid-phase combinatorial libraries. CHI Human Proteome. January 12, 2005

2. *J. T. Lathrop.* New Biomarker and Target Discovery from the Human Plasma Proteome CHI Biomarkers. Philadelphia, PA. August 26, 2003 (invited oral presentation).

3. *J. T. Lathrop*, J. Sarkar, A. McKeague, S. Soukharev, L. McKenzie, Kris Sachsenmeier, L. Cowsert, D. Hammond. Novel Methods for Elucidating the Function of Plasma Proteins. Presented at the Blood Safety and Production meeting, June 9, 2003, Reston, VA.

4. *J. T. Lathrop*, J. Sarkar, A. McKeague, S. Soukharev, L. McKenzie, Kris Sachsenmeier, L. Cowsert, D. Hammond. Functional Identification of Novel Activities- Mining the Plasma for New Therapeutic Proteins. Presented at the Plasma Products Biotechnology 2003 meeting, Curacao, April 23, 2003

5. *Lathrop, J.T.*, Chihos, T.J., Riley, J., Li, Z-M., Gheorghiu, L., and Mann, D. Human Fibrin Sealant for Local Drug Delivery. Presented at the 11th annual open scientific meeting of the Musculoskeletal Infection Society, August 2-4, 2001. Snowmass, CO.

6. *Lathrop, J.T.* Human Fibrin Sealant as a Matrix for Local Drug Delivery. Presented at the 2nd Plasma Products Biotechnology meeting, May 14-18, 2001. Malta

7. *Lathrop, J.T.* New Technologies: Supplemented Fibrin Sealant. Presented at the Liquid Fibrin Sealant Advisory Board meeting, April 17 - 18, 2000. Washington, D.C.

8. *Lathrop, J.T.*, Chihos, T. J., Tuthill, D., Friedman, S., Davis-Bruno, K., Rudnicka, K., Beall, D., and MacPhee, M. *Ex Vivo* Porcine Arteriotomy Assay: A Functional Assay for Characterizing a Fibrin-Sealant Bandage. Emerging Application of Tissue Sealants Meeting, San Diego, CA. May, 1999.

ABSTRACTS AND POSTERS

1. Jolly Sarkar; David Hammond, *Julia Tait Lathrop*; Identification of Growth factors by functional selection on combinatorial libraries of affinity ligands. 4th annual HUPO meeting, August 29- Sept 1, 2005, Munch, Germany.

2. Luc Guerrier; Frederic Fortis; Shanhua Lin; Steve Roth; Lee Lomas; *Julie Lathrop*; David Hammond; Egisto Boschetti; Scot Weinberger; and Vanitha Thulasiraman: Novel method of reducing dynamic range of proteins in human serum proteome using a combinatorial library of solid phase ligands. CHI Beyond Genomics meeting, June 15-16, 2005 (selected for oral presentation by Vanitha Thulasiraman)

3. Shanhua Lin; Vanitha Thulasiraman; Steve Roth; Lee Lomas; Scot Weinberger; *Julia Lathrop*; David Hammond; Egisto Boschetti: A novel, combinatorial ligand library used to address protein dynamic range detection challenges of human serum. American Society of Mass Spectrometry, June 6-9, 2005. San Antonio, TX.

4. *Julia Lathrop*, Liliana Gheorghiu, Shanhua Lin, Lee Lomas, Jolly Sarkar, Vanitha Thulasiraman Egisto Boschetti, David Hammond. New Method of reducing the concentration

range of proteins in serum using a combinatorial library of solid phase ligands. CHI Biomarker World Congress, Philadelphia, PA; May 23-25, 2005

5. *Julia Lathrop*, Lee Lomas, Serguei Soukharev, Egisto Boschetti, and David Hammond. Specific enrichment of trace plasma proteins for detecting contaminants and identification of new biological activities. Plasma Products Biotechnology, May 9-12, 2005, Crete, Greece.

6. L. Gheorghiu; *J. Lathrop*, L. Lomas, V. Thulasiraman, D. Hammond, E. Boschetti. Exploring the Proteome III, NIH, Bethesda, MD; April 15, 2005. New Method of reducing the concentration range of proteins in serum using a combinatorial library of solid phase ligands. Exploring the Proteome III, NIH, Bethesda, MD; April 15, 2005

7. L. Lomas, V. Thulasiraman, S. Lin, L. Gheorghiu, *J. Lathrop,* D. Hammond, E. Boschetti .Novel Method of Reducing the Concentration Dynamic Range of Proteins in Serum using a Combinatorial Library of Solid-Phase Ligands.. Presented at Microseparations Conference, New Orleans, LA, Feb. 14, 2005.

8. D. J. Hammond, S. Soukharev, *J.T. Lathrop*, Functional Identification of Novel Activities: Mining Plasma for New Therapeutics. 6th Siena Meeting: From Genome to Proteome, Siena, Italy, Aug. 30, 2004.

9. Jolly Sarkar, Kevin Carrick, Tim Hayes, David Hammond, *Julia Tait Lathrop;* Functional Identification of Novel Activities: Discovery of Novel Growth Factors. Poster presented by Jolly Sarkar at FASEB, Washington, D.C., April 19, 2004.

10. Kris F. Sachsenmeier, *Julia Tait Lathrop*, Jolly Sarkar, Darrin W. Sabol, Lorraine R. McKenzie, Kevin Sullivan and Lex M. Cowsert Target Independent Antibody Discovery , Antibody Engineering: Forging the Future of Antibody Therapeutics. November 2003, San Diego, CA

11. Kris F. Sachsenmeier, *Julia Tait Lathrop*, Jolly Sarkar, Darrin W. Sabol, Lorraine R. McKenzie, and Lex M. Cowsert. Target Independent Antibody Discovery. Drug Discovery Technology® World Congress, August 2003, Boston, MA

12. K F Sachsenmeier, *J.T. Lathrop,* J. Sarkar, D. W. Sabol, L. R. McKenzie, and L. M. Cowsert In vitro quantification of disease phenotypes: an automated system for drug discovery. (Presented by L. Cowsert) Plasma Products Biotechnology 2003 meeting, Curacao, April 23, 2003.

13. *Lathrop, J.T.,* Chihos, T. J., Tuthill, D., Friedman, S., Davis-Bruno, K., Rudnicka, K., Beall, D., and MacPhee, M. *Ex Vivo* Porcine Arteriotomy Assay: A Functional Assay for Characterizing a Fibrin-Sealant Bandage. First Plasma Products Biotechnology Meeting, Daydream Island, Australia, August, 1999 (by Martin MacPhee).

14. *Lathrop, J.T.* and Timko, M.P., Identification of amino acids mediating hemin regulation of erythroid preALAS import into mouse mitochondria. Poster presented at the 1992 Gordon Research Conference on Pyrrol Compounds. Selected for oral presentation.

15. *Lathrop, J.T.,* and Dierks, P.M. Hemin inhibition of in vitro transport of erythroid preALAS into mouse mitochondria. Poster presented at the 1990 Gordon Research Conference on Pyrrol Compounds.